UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

To: Jennifer Gaines

From: Eric Bohnenblust, Ph.D., Entomologist

Secondary Review: Pesticide Efficacy Review Committee (PERC)

Date: June 3, 2015

Subject: PRODUCT PERFORMANCE DATA EVALUATION RECORD (DER)

THIS DER DOES NOT CONTAIN CONFIDENTIAL BUSINESS INFORMATION

Note: MRIDs found to be **unacceptable** to support label claims should be removed from the data matrix.

DP barcode: 427473
Decision no.: 499382
Submission no: 963336
Action code: R340
Product Name: RF9908 Spot On
EPA Reg. No or File Symbol: 2724-497
Formulation Type: Spot-On
Ingredients statement from the label with PC codes included:
S-Methoprene 3.0 % PC: 105402
Permethrin 45.0 % PC: 109701
Application rate(s) of product and each active ingredient (lbs. or gallons/1000 square feet or per acre as appropriate; and g/m^2 or mg/cm^2 or mg/kg body weight as appropriate):
0.022 fl. oz. for dogs 7-15 lb. (100 - 214 mg product/kg body weight, 45.0 – 96.3 mg Permethrin/kg body weight, 3.0 – 6.42 mg S-methoprene/kg body weight)
0.034 fl. oz. for dogs 16-30 lb. (77.2 - 144 mg product/kg body weight, 34.8 – 64.8 mg Permethrin/kg body weight, 2.3 – 4.32 mg S-methoprene/kg body weight)
0.068 fl. oz. for dogs 31-60 lb. (77.2 - 150 mg product/kg body weight, 34.8 – 67.5 mg Permethrin/kg body weight, 2.3 – 4.5 mg S-methoprene/kg body weight)
0.101 fl. oz. for dogs over 60 lb. (113.1 mg product/kg body weight, 50.91 mg Permethrin/kg body weight +, 3.4 mg S-methoprene/kg body weight +)
Use Patterns: Spot On

I. Action Requested: This is a rebuttal to an efficacy review dated May 7, 2015 which denied the addition of new efficacy claims against ticks, lice, mosquitoes, and fleas.

II. Background: The product is currently registered and is labeled to kill and repel fleas, ticks, and mosquitoes, the product also is labeled with insect growth regulator claims for efficacy against flea eggs and larvae. MRIDs 46006001 and 46006002 were previously reviewed (DP 291571) to support this product and MRID 46006002. In the review for DP 291571, MRID 46006002 was rated as supplemental and requested that data supporting claims against mosquitoes be submitted to the Agency. Despite the review that did not support the inclusion of mosquito

claims on the label, mosquito claims were granted by the Agency. This is a rebuttal to an efficacy review dated May 7, 2015 (DP 425605) which denied the addition of new efficacy claims against fleas, lice, mosquitoes, and brown dog tick, American dog tick, deer tick, and lone star tick. In addition the review DP 425605 asked the registrant to remove all claims against mosquitoes.

III. EPA Response to Rebuttal Points

1. As a minor point, in regards to (p.1) **Application rate(s) of product and each active ingredient:** Three treatment groups were listed, there should be a fourth: 1.01 fl. oz. for dogs over 60 lb

EPA Response: We note the missing information which is 0.101 fl. oz for dogs over 60 lb and added it to the administrative information in this rebuttal to reflect all of the weight classes.

2. RE: 46006002. Efficacy of a Permethrin and Pyriproxyfen Product for Control of Fleas, Ticks and Mosquitoes on Dogs.
(1) **Conclusion: Supplemental.** This MRID was deemed supplemental and does not support any label claims because the study tested a 45% permethrin and 5% Nylar (pyriproxyfen) product which is different from the proposed product.

Wellmark Response: MRID 46006002 is a 1997 journal article report of an efficacy study conducted with product with EPA Reg. No. 270-278. The mechanism of action of permethrin (to disrupt sodium channels) is distinct from that of pyriproxyfen, which is a juvenile hormone mimic. Therefore, it is considered that the adulticide efficacy of permethrin in one formula can be bridged to the other product. Dose levels in the Farnam product are generally higher than those in the Wellmark Product, but the ranges do overlap, and for some weights, the dose of the Wellmark product is higher. See Table 1 for a comparison of doses between the two products.

EPA Response: We agree with Wellmark's argument that the mechanism of action of permethrin and pyriproxfen are distinct. We also acknowledge that that pyriproxyfen alone does not have adulticidal effects on adult fleas, ticks, and mosquitoes. However, data were not submitted showing that adding pyriproxyfen to permethrin does not increase efficacy against these pest groups.

Although pyriproxyfen may not have direct adulticidal effects on adult insects including fleas, pyriproxfen does cause sublethal effects such as reducing lifespan and fecundity, and ovisterilization (Dryden and Rust 1994, Meola et al. 2000). Therefore, studies that support the proposed claims must examine the effects of the adulticide and insect growth regulator (IGR) components separately because the IGR may impact adult survivorship, and possibly enhance the control provided by permethrin.

Moreover, the data are not product specific. The product these studies are intended to support is a combination of permethrin and methoprene. The product tested in this study is a combination of permethrin and pyriproxyfen. Because pyriproxyfen can have sub-lethal effects on on adult insects, we cannot bridge the data from this study to support a product that contains methoprene instead of pyriproxyfen. The Agency requires product specific data for efficacy, in the case of the proposed adulticide claims, only data showing efficacy of the adulticide ingredient should be submitted for evaluation by the Agency to support the requested adulticide claims.

Because the data are not product specific, the rate table is not applicable to this rebuttal.

3. RE: **43111607. In Vitro Toxicity and Repellency of Hartz Mountain Dermal Treatment (TS#10009) to Deer Ticks (*Ixodes dammini*) as compared to Brown Dog Ticks (*Rhipicephalus sanguineus*).**
Conclusion: Supplemental. This study alone does not support any efficacy claims. This study does not support kill claims because moribund and dead ticks were not separated.

Wellmark Response: I understand that, especially for short-term exposures to some insecticides, insects that appear moribund can recover. However, we are not aware of documentation that ticks exposed to permethrin and found

moribund after 24 hours will later recover. Lacking that, we expect that ticks moribund at 24 hours will end up as dead, and so counting them as dead at 24 hours would be valid.

EPA Response: The agency does not consider moribund subjects to be dead. Therefore documentation of moribund subjects does not meet our efficacy criteria. We do consider morbidity for knockdown efficacy claims provided that data at subsequent timepoints confirm the moribund subjects died after being classified as moribund.

4. 46498301. Efficacy of Various Ectoparasticide Products Against Mosquitoes on Dogs.
(1) Conclusion: Unacceptable. Mosquito landings were only reduced by 50%; therefore, repellency claims are not supported by this study. Moribund mosquitoes were considered dead in the study, the Agency only considers dead insects when assessing efficacy. Further, the rates tested are in the middle of the rate range on the registered product and the tested product is different than the registered product. Also, the agency requires a minimum of 6 dogs for replication.

Wellmark Response: As discussed in our phone conference, the 96.5% reduction in blood feeding should be considered as evidence for repellency. While it is acknowledged that this is not the standard that is used for humans, it is still the accepted standard for pets.
Further, the guideline OPPTS 810.3300 does not always require 6 animals per group, it requires statistical significance. Since this was a GLP study, the data should be acceptable. The application rate comment is the same as for MRID 46006002 above.

EPA Response: We acknowledge that blood feeding will be considered as evidence for repellency for pet products. However, the substance tested in the study was a combination product containing permethrin and pyriproxyfen, please see our argument under rebuttal point two regarding why this study cannot be bridged to support the combination permethrin and methoprene product. In addition, if fewer than 6 animals per group are to be tested then a statistical justification for the smaller sample size must be clearly articulated.

5. 44945503. A Study to Measure the Efficacy of an IGR Product Against Fleas on Dogs.
(1) Conclusion: Unacceptable. The rates tested in this study are higher than the labeled rate on the product. Dogs were not inoculated with fleas until 13 days after treatment, inoculations and counts should begin within 48 h of treatment.

Wellmark Response: We are skeptical that 48.9% permethrin is an acceptable reference for the amount of permethrin in the test substance. The Hartz Mountain product supported by this study was 45% permethrin, and 48.9% is outside the upper certified limit for a 45% permethrin product. (i.e., it would be a GLP violation to use a 48.9% permethrin product in a study to support a 45% product.) It is more likely that 48.91% represents the formulation level of a 92% technical (48.91 x 0.92 = 44.997).
In regards to inoculation with fleas at 13 days after treatment, we are not aware of a requirement to begin inoculations 48 hours after treatment. When short-term time points are not critical to the outcome of the study (in the case that residual claims are being tested) elimination of those data points would seem to be a valid cost-cutting measure. Wellmark routinely skips short term data points for S-Methoprene, for example, and EPA has not objected before now.

EPA Response: The test sample identification page in MRID 44945503 indicates that the tested sample product is a 48.91% permethrin and 3.09% S-methoprene product and the registered product is a 45% product and the test substance was applied at the same or higher volumes than which the registered product is labeled for application. If short-term data points are skipped, then justification should be provided for skipping them.

6. 43137202. Hartz Mountain Short Term Efficacy Study on Dogs.
(1) Conclusion: Unacceptable. This study does not support efficacy claims for the labeled product because the tested rate of permethrin is higher than the labeled rate. Additionally the first inoculation after treatment was made on day 7. Initial count of the tested organism should be made within 48 hours of treatment. Moreover, efficacy after

day 21 was less than 90% therefore 1 month efficacy claims are not supported.

Wellmark Response: For this study, the response to the comment about the application rate is the same as that above. In addition, the response to the comment about inoculation timing is also the same as above. Question – was evaluation based on flea counts alone or on Abbott's formula?

EPA Response: Because the 47.26% product fall within the certified limits, the application rate is acceptable for all dogs in the study over 16 lb; however, efficacy was less than 90% after day 21, the Agency requires efficacy through a 28 day inoculation for one month efficacy claims. Regardless of whether we use Abbott's formula or flea counts, efficacy does not reach 90% after 21 days. In addition, unknown numbers of fleas and ticks were inoculated which means we cannot evaluate flea counts based off of initial inoculation numbers.

7. 43137203. Hartz Mountain Repellent Study-Dogs.
(1) Conclusion: Unacceptable. This study does not support efficacy claims for the labeled product because the tested rate of permethrin is higher than the labeled rate. Also, the number of fleas/ticks used to infest each dog were not specified. Moreover, this study does not support repellency claims because data showing repellency were not collected.

Wellmark Response: For this study as well, the response to the comment about the application rate is the same as that above. My interpretation of the study design is that repellency is inherent in the study design. Having two adjacent runs and fleas and ticks in the middle allows for an even distribution of fleas and ticks. Untreated, one would expect the organisms to split 50/50, but the fact that treated dogs picked up fewer pests implies repellency. The total number of fleas and ticks released is immaterial since what is measured is what is on the animals. If anything, since animals could fall off a treated dog (and not be counted), study bias is in favor of non-treated dogs, suggesting the results are understated.

EPA Response: Because the 47.26% product fall within the certified limits, the application rate is acceptable for all acceptable for all dogs in the study over 16 lb; however, the study is still unacceptable because efficacy against fleas is inadequate and because we do not know the number of fleas and ticks that were released. Because the number of fleas and ticks released we do not know what percentage of the total made it onto the different animals. This is problematic for showing repellency, because if large numbers of individuals were not attracted to either animal then they are neither repelled nor attracted. We have to consider that a choice of neither animal is still a choice. Moreover, we also do not know if fleas and ticks went towards treated animals and turned away or just never went in the direction at all. If they went towards the animal and turned away this could indicate repellency; however, if they rarely went in the direction of a treated animal this could be caused by confounding factors in the experiment that influence host seeking behavior. In addition, while this study suggests repellency against fleas might be occurring, efficacy is only shown through 16 days post application. The Agency requires 90% efficacy through a 28 day inoculation to support month long efficacy claims. While tick repellency was 90% for 30 days, repellency claims against ticks are not acceptable because the methods are not sufficient to determine repellency.

8. 002596-137
43111607 Neunteufel, E.; Goldman, K. (1993) In vitro Toxicity and Repellency of Hartz Mountain Dermal Treatment (TS#10009) to Deer Ticks (Ixodes dammini) as Compared to Brown Dog Ticks (Rhipicephalus sanguineus): Lab Project Number: RNB/1226/50. Unpublished study prepared by The Hartz Mountain Corp. 26 p.
43137202 Hartz Mountain Corp. (1993) Hartz Mountain Short Term Efficacy Study on Dogs: (Hartz One Spot Repellent for Dogs): Lab Project Number: 1210. Unpublished study. 15 p.
43137203 Hartz Mountain Corp. (1993) Hartz Mountain Repellent Study-Dogs: (Hart One Spot Repellent for Dogs): Lab Project Number: 1218. Unpublished study. 16 p.

EPA Response: This product is canceled therefore these MRIDs no longer support claims for this product.

002596-146, 002596-147
44945503 Glass, R. (1999) A Study to Measure the Efficacy of an IGR Product Against Fleas on Dogs Test. Unpublished study prepared by Hartz Mountain Corporation and Sharp Veterinary Research. 16 p.

EPA Response: The 2596-146 product is canceled therefore this MRID no longer supports claims for this product. The 2596-147 product is a cat product and dog studies are not acceptable to support cat products, so this MRID should not support claims for this product and claims on this product and we will not bridge claims from cat products to dog products.

073510-2
45364808 Fourie, L.; Kok, D. (2000) Efficacy and Residual Insecticidal Activity of Two Topical Formulations, One Containing 45% w/w Permethrin Cis: Trans 25:75 (Formulation A) and One Containing 65% w/w Permethrin Cis: Trans 25:75 (Formulation B), Against Infestation of Adult Ctenocephalides felis and Ripicephalus sanguineus on Dogs: Lab Project Number: BIL CV6. Unpublished study prepared by ClinVet International. 72 p.
46039501 Cruthers, L. (2003) Efficacy Evaluation of a Permethrin Squeeze-On Against Adult Cat Fleas (Ctenocephalides Felis), Adult Brown Dog Ticks (Rhipicephalus Sanguineus), Nymphal Deer Ticks (Ixodes Scapularis) and Adult Aedes aegypti Mosquitoes on Dogs. Project Number: 0243. Unpublished study prepared by Professional Laboratory and Research Services, Inc. 79 p.
46425801 Horton, R. (2004) Product Performance: Treatments to Control Pests of Humans and Pets: (MarketQuest One Drop Flea & Tick Control). Unpublished study prepared by Marketquest Inc. 48 p.

EPA Response: This product is canceled therefore this MRID no longer supports claims for this product.

V. LABEL RECOMMENDATIONS:

(1) No new marketing claims are supported by the MRID's above. Please see labeling comments from the review for DP 425605.